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PATENT
Docket No. 2710-4007US2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Michael B. CHANCELLOR et al.

Serial No. : 09/549,937

Filed : April 14, 2000

Art Unit : 1635

Examiner : Brian A. Whiteman

For : **Soft Tissue and Bone Augmentation and Bulking Using Muscle-Derived Progenitor Cells, Compositions and Treatments Thereof**

Commissioner for Patents
Washington, D.C. 20231

Declaration of Michael Chancellor, M.D. under 37 C.F.R. §1.132

I, Michael Chancellor, M.D., hereby declare and state that:

1. I am an inventor of the subject matter described and claimed in the above-identified patent application.

2. I am a member of the faculty in the Department of Urology at the University of Pittsburgh School of Medicine, Pittsburgh, PA. As part of my responsibilities as a physician and faculty member, I perform clinical studies and direct and carry out research, primarily in the field urological dysfunction. The research in my laboratory focuses on developing and testing new treatments and therapies for diseases and disorders in the field of urology, with an emphasis on stress urinary incontinence (SUI). In collaboration with my colleagues, I and my laboratory researchers perform research in the areas of muscle-derived cell-based treatments for a variety of different

muscle-related disorders using animal (rat and mice) model systems. In particular, animal models of SUI are studied to discover new treatments and therapies for SUI and related disorders, as well as to assess muscle derived progenitor cells (MDC) in bulking and augmentation treatments for muscle-related (e.g., smooth and non-smooth muscle) injuries, disorders, or dysfunctions.

3. I have reviewed the above-identified patent application and claims, and have read and understood the complete contents of the non-final office action mailed from the U.S. Patent and Trademark Office on May 22, 2002, including the Examiner's comments and rejections of the claims at pages 2-18 of the Detailed Action.

4. In the office action, the examiner has rejected claims 1-3, 17-27, 45-55, 84 and 92-96 under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that, at the time the application was filed, the inventors had possession of the claimed invention.

5. Based on my own experimental work and knowledge in the field, I submit that the muscle derived progenitor cells (MDC) as presently claimed are described in the instant application so as to be able to be made from animals other than mice and used by a person having skill in the pertinent art . The specification teaches at page 14, that MDC can be isolated from mammalian skeletal muscle explants using the pre-plating technique as described and claimed in the application. (See, Example 1, pages 28-29). There is no indication that the MDC are isolatable only from mice. Page 29,

Example 1, of the specification discloses that MDC were isolated from explants of *mdx* (dystrophic) mice, normal female SD (Sprague Dawley) rats, or SCID (severe combined immune deficient) mice. Experimental work conducted by my laboratory, my co-inventors and research workers, and based on the teachings in the disclosure of the instant specification demonstrates that MDC can be isolated from a variety of mammalian species, including, rodents, rabbits and even humans. Such MDC have been demonstrated to have properties of long-term survivability, proliferation and function for greater than about two weeks following injection into a muscle tissue area of a recipient host.

6. The specification provides sufficient guidance to enrich for and isolate MDC from animal muscle sources other than those of mice, and to use those cells as clearly described in the instant application. The specification provides methods to assess the long-term viability and survival, as well as functioning, of the MDC, regardless of the species from which they are derived. It has been demonstrated, both in the specification, and in our continuing research in this field, that MDC can repopulate an area of muscle tissue into which they are introduced and function following injection for both short and long periods of time. Study of the mechanism of function may be ongoing; however, the mechanism need not be known in order to isolate the MDC and practice the invention as presently claimed. The MDC from several species have been shown to survive viably for weeks and months following *in vivo* injection into muscle tissue; this long-term survival allows the cells to assimilate into their transplanted milieu and develop and function appropriately.

7. Based on my own experimental research and information known to me, I maintain that the MDC as described in the instant specification and as isolated by our pre-plating technique advances the art of cell transplantation by using a not-before described population of MDC to augment and bulk muscle tissue and improve muscle strength. The approach of using MDC to treat and affect muscle tissue weakness, injury, disorders and dysfunction overcomes the problems previously encountered using other techniques or materials in the art, for example, immune rejection, poor cell survival and limited spread of injected cells. The applicability of the use of MDC for introduction into a variety of muscle tissues is demonstrated in the instant application (e.g., Examples 3-8, pp. 32-40 of the instant specification). Since the filing of the instant application, much experimental work, based on the teachings of the application, has been conducted. The results of this work support the originally presented experiments, and representative examples are provided in the abstracts enclosed with the response. The abstracts demonstrate that MDC exhibit survival and myotube formation co-localize with a cardiac specific α-myosin heavy chain at over 36 weeks post injection into host myocardium (H. Oshima et al., 2002, Exhibit 13 provided with the response), and that MDC injected into recipient heart deliver dystrophin within the heart at 8 weeks post injection (T. Payne et al., 2002, Exhibit 14 provided with the response).

8. The Examiner states that it is not apparent how an increase in the contractility of cryodamaged bladder tissue in rats using MDC reasonably correlates to a method of treating weakness or dysfunction in muscle tissue in mice using muscle

derived cell therapy. (detailed office action, p. 9). Cryodamaged bladder tissue and damaged or dysfunctional sphincter muscle constitute examples of injured and dysfunctional muscle tissue which are associated with stress urinary incontinence (SUI). The experiments carried out in mice and rats using MDC according to the invention show that the MDC can repair the damage done to the bladder or sphincter muscle tissue and surrounding nerves as assessed at a long time following injection into the bladder or sphincter. Other experiments using MDC to repair sphincter damage support the use of the MDC of the invention for the treatment of weak, injured or dysfunctional muscle tissue. Further, in the model system used, it is understood and appreciated by the skilled practitioner that a finding of an increase in contractility of bladder strips obtained from the damaged bladder tissue following MDC introduction in rats, and increased fiber production, demonstrate the viability and function of the MDC following injection into such muscle tissue. This is because muscle contraction is an indicator of proper muscle and associated nerve function. The restoration of bladder muscle contractility following disruption of the muscle, and increased fiber production, show that the introduced MDC have affected muscle and nerve tissue repair and augmentation.

9 a). To investigate the pathophysiology and treatment of SUI, a disorder affecting muscle tissue, animal models of decreased urethral resistance have been developed. These animal models represent a reproduction of the primary etiological factor associated with human SUI vaginal parity, and its effects on both the neuromuscular and connective tissue properties of the pelvic floor. As a consequence, two basic categories of animal models have been developed including nerve injury

models and simulated birth trauma models.

9 b). Nerve injury models include pudendal nerve transection models and the pudendal nerve crush model. These models were established to approximate the injury sustained clinically during human vaginal delivery. Histological studies of the rat urethra following bilateral pudendal nerve transection demonstrated urethral skeletal muscle atrophy (M.C. Heidkamp et al., 1998, *Int. Urogynecol. J.*, 9:88-93, Exhibit 6 as provided with the response). Although cystometric and histological changes are demonstrated in the nerve trauma rat model, the simulated birth trauma rat model more reliably reproduces the injuries sustained during vaginal child delivery (See, e.g., A.S. Lin et al., 1998, *Urol.*, 52:143-151, Exhibit 16 as provided with the response).

9 c). The simulated birth injury model in rats was developed to evaluate the effects of vaginal distension on the urinary continence mechanism (A.S. Lin et al., *Ibid.*, Exhibit 16). Modified foley catheters are inserted into the vaginas of anesthetized female rats and inflated as a simulation of the trauma of vaginal delivery on the pelvic floor. Histological studies have demonstrated pathologic damage to the pelvic ganglia, levator muscles and urethra which closely reapproximate the pelvic floor, urethral sphincter and neurologic damage sustained during human vaginal delivery. Such animal models, which are considered in the art to closely approximate the human condition, serve as art-recognized systems in which to test treatment methods and therapies for the muscle-associated affliction of SUI.

9 d). As further support for rats as art recognized and accepted animal models for the use of MDC in the treatment of muscle weakness or dysfunction and in augmenting and bulking up muscle tissue, I am currently engaged by Roche Pharmaceuticals – Palo Alto and Pfizer Pharmaceutical, Inc. and have been working with these companies for over a year to study and test potential therapeutic agents to treat genitourinary disorders, such as urinary incontinence and/or bladder outlet obstruction, which involve muscle tissue weakness or dysfunction. These companies have recognized and embraced studies that utilize female SD rats as appropriate animal models to extrapolate results of functional assays for incontinence and bladder outlet obstruction to other mammalian species, including human females, which have similar muscle-related weaknesses and disorders.

10. Based on knowledge and belief, I maintain that the isolation and use of MDC for the diverse muscle tissue based treatment applications as described in the instant specification would not require an undue or unreasonable amount experimentation by a person having skill in this art. MDC isolated and used as described can augment, bulk, or treat numerous types of smooth and non-smooth muscle injury, weakness, or dysfunction (e.g., myocardium, bladder, urethra, sphincter, spleen, liver) following the methods disclosed in the application and as appropriate for a given type of muscle tissue. Practice of the claimed invention is as straightforward as enriching and isolating MDC, e.g., using the preplating technique as taught and claimed,

and then injecting a physiologically acceptable preparation of the isolated MDC into a site of muscle tissue in need of repair. The immunotolerant nature of the MDC and their developmental plasticity according to this invention allow the MDC to remain viable, to repopulate and function in the tissue environment in which they have been introduced. Successful practice of the claimed invention is within the capability and know-how of the skilled practitioner with no requirement for undue or unreasonable experimentation. Subsequent to MDC injection into a site of muscle tissue, the injected cells can be tracked, as warranted, after varying periods of time and assessed for their survival and function using routine techniques, which also do not involve undue experimentation.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 11/19/02 By: _____

Michael B. Chancellor, M.D.